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BEFORE THE BOARD OF PATENT APPEALS AND INTERFERENCES

Application Number: 09/903,412
Filing Date: July 11, 2001
Appellant(s): KOIDE, SHOHEI

Peter Malen
For Appellant

EXAMINER'S ANSWER

This is in response to the appeal brief filed 4/2/2007 appealing from the Office action mailed 6/9/2006.

(1) Real Party in Interest

A statement identifying by name the real party in interest is contained in the brief.

(2) Related Appeals and Interferences

The examiner is not aware of any related appeals, interferences, or judicial proceedings which will directly affect or be directly affected by or have a bearing on the Board's decision in the pending appeal.

(3) Status of Claims

The statement of the status of claims contained in the brief is correct. This appeal involves claims 1, 4, 7-8 and 54-63.

(4) Status of Amendments After Final

The appellant's statement of the status of amendments after final rejection contained in the brief is correct.

No amendment after final has been filed.

(5) Summary of Claimed Subject Matter

The summary of claimed subject matter contained in the brief is correct.

(6) Grounds of Rejection to be Reviewed on Appeal

The appellant's statement of the grounds of rejection to be reviewed on appeal is substantially correct. The changes are as follows: the rejections under 35 USC 112, first paragraph, new matter and written description are withdrawn. Only the 35 USC 103 rejections are at issue.

(7) Claims Appendix

The copy of the appealed claims contained in the Appendix to the brief is correct.

(8) Evidence Relied Upon

6,818,418 LIPOVSEK

W0 98/56915 KOIDE

Spector, S. "Rational modifications of Protein stability by the mutation of charged surface residues", Biochemistry, 2000, vol. 39, pp. 8720879.

(9) Grounds of Rejection

The following ground(s) of rejection are applicable to the appealed claims:

Claims 1, 4, 7-8 and 54-63 are rejected under 35 U.S.C. 103(a) as being unpatentable over Koide (WO 98/56915) or Lipovsek et al (USP 6,818,418) in view of Spector et al (Biochemistry).

Koide discloses at page 6, lines 12-26 a fibronectin (Fn3) polypeptide monobody comprising a plurality of Fn3 beta-strand domain sequences that are linked to a plurality of loop region sequences. One or more of the monobody loop region sequences of the Fn3 polypeptide vary by replacement of at least two amino acids from the corresponding loop region sequences in wild-type Fn3. One or more of the loop regions of the monobody comprise amino acid residues: i) from 15 to 16 inclusive in an AB loop; ii) from 22 to 30 inclusive in a BC loop and in the other loops (which encompasses the claimed amino acid at position 23). Koide discloses that 17 Fn3 domains are present just in human fibronectin that provides important information on conserved residues which are often important for the **stability** and folding. Large variations are seen in the BC and FG loops, Example XVII, page 51. See further the Examples, specifically the Tables.

Lipovsek discloses at e.g., col. 9, line 24 up to col. 10, line 68 a human 10Fn3 sequence that can be randomized, at a minimum, at amino acids 1-9 (which includes the claimed 7 and 9 positions), 44-50, 61-54, 82-94 (edges of beta sheets); 21-31 (which includes the claim 23 position), 51-56, 76-88 (CDR-like solvent-accessible loops) and other solvent-accessible loops and beta turns to evolve new or improved compound-binding, **stable** proteins (col. 2, line 10). The mutations change the scaffold and thereby indirectly alter loop structure(s). Lipovsek discloses that if this approach is taken, mutations should not saturate the sequence, but rather few mutations should be introduced. Preferably, no more than 10 amino acid changes, and, more preferably, no more than 3 amino acid changes should be introduced to the beta-sheet sequences. (Lipovsek at col. 18, lines 34-45). Each of Koide or Lipovsek teaches stable modified Fn3. However each of these references does not teach that the regions containing e.g., amino acids 7, 9 or 23 are involved in an unfavorable electrostatic interaction, as claimed. Spector teaches at e.g., page 872 several of the residues that are involved in the destabilization of the overall stability of a small residue region of a protein. Spector picked to modify position 8, one of the residues of the helical protein that makes a significant, unfavorable electrostatic contribution to

the overall stability of a protein. Spector teaches that replacement of this residue with Nle or adipic acid results in a **more stable** protein than the wild-type protein. Spector further teaches at e.g., page 873 and page 879 that the results of their study suggest a general strategy for increasing the stability of a protein by minimizing unfavorable surface interactions. Many proteins contain clusters of positively or negatively charged residues and the results presented therein suggest that optimization of surface electrostatic interactions are likely to be a generally applicable strategy for enhancing protein stability. Accordingly, it would have been obvious to one having ordinary skill in the art at the time the invention was made to determine whether amino acid residues at e.g., 1-9 or 21-31 of the Fn region of Lipovsek or Koide is involved in an unfavorable electrostatic interactions as taught by Spector. Since the interactions produces instability to a loop region of the protein hence, one would be motivated to modify these wild-type residues. The modification of these residues by any amino acid (e.g., by replacement of amino acids) is taught by e.g., Lipovsek.

(10) Response to Argument

Appellant recognizes that Koide relates to Fn3 polypeptide monobodies. Applicants argue that only mutant fibronectin

molecules with reduced stability relative to wild type fibronectin are disclosed in Koide (e.g., Figure 16 and Example XVII).

In reply, whether the stability is reduced is immaterial. The fact is, as applicant recognizes, the compound is known. Also, the claims do not preclude Fn3 with said reduced stability.

Appellant recognizes that Lipovsek relates to antibody mimics that are based on the structure of an Fn3 (column 7, lines 63-65). Appellant states that Lipovsek teaches that for the human 10Fn3 sequence, at a minimum, amino acids 1-9, 44-50, 61-54, 82-94 (edges of beta sheets); 19, 21, 30-46 (even), 79-65 (odd) (solvent-accessible faces of both beta sheets); 21-31, 51-56, 76-88 (CDR-like solvent-accessible loops); and 14-16 and 36-45 (other solvent-accessible loops and beta turns) may be randomized to evolve new or improved compound-binding proteins (column 9, lines 24-31). But argues that Spector relates to the electrostatic contributions that charged and polar side chains make on the overall stability of a 41-residue protein (first sentence of the Abstract), a protein that is based on the peripheral subunit-binding domain, derived from the dihydrolipoamide acetyltransferase component of the pyruvate dehydrogenase multienzyme complex from Bacillus

stearothermophilus (page 873, first column, second full paragraph).

Appellant submits that Spector does not remedy the deficiencies of Koide and Lipovsek because Spector does not teach or suggest that the regions of Fn3 containing amino acids 7, 9 or 23 are involved in an unfavorable electrostatic interaction.

In reply, appellant cannot attack the references individually when the rejection is based on the combination of references. It is Lipovsek and Koide that teach a stable Fn3 compound, when modified in the loop region. Spector is employed for its teaching that destabilization of protein is due to the unfavorable electrostatic interactions of amino acids in the loop region of the protein. These amino acids are either adjacent to each other or from a nearby loop region. Spector further teaches that replacing these unfavorable amino acids e.g., at positions 8 and 9 would produce a stable protein.

Spector discloses, throughout the article, at e.g., page 875, col. 1 up to col. 2, first complete paragraph:

> The calculations suggest that three residues, **Arg8**, **Lys9**, and Asp36, make a significant unfavorable electrostatic contribution to the overall stability of the peripheral subunit-binding domain. Of these, **Arg8 was chosen to test the results of the calculations**. It is located on the surface of the peripheral subunit-binding domain in a region of strong positive electrostatic potential (Figure

> 2). **Arg8 is the second residue in a helix, and therefore, its charged guanidino group may interact unfavorably with backbone dipolar groups in the helix.** In addition, there is another arginine on the same face of the helix at position 12, four residues away from Arg8, and these two residues could also interact unfavorably. Replacement of Arg8 with a hydrophobic residue should eliminate these unfavorable electrostatic interactions. Substitution with a negatively charged residue could provide further stability through favorable salt-bridge and backbone dipole interactions, as well as through other interactions with the local positive potential…. (Emphasis added).

Spector further discloses at e.g., page 879, col. 1:

> The substitutions were made in the context of a model study….. the methodology could… be applied to other proteins if care is taken to avoid residues involved in catalysis or intermolecular interactions. Relatively little attention has been paid to the contributions of surface electrostatic interactions to the stability of globular proteins. This study provides a clear demonstration that alleviating unfavorable surface interactions can increase the stability of proteins. Many proteins contain clusters of positively or negatively charged residues, and the results presented here suggest that optimization of surface electrostatic interactions is likely to be a generally applicable strategy for enhancing protein stability..

Thus, the combined teachings of the prior art would lead one having ordinary skill in the art to the claimed modified and stable Fn3 compound. Lipovsek teaches a modified and **stable Fn3** wherein positions 1-9 (which encompasses the claimed 7 and 9 positions) and positions 21-31 (which include the claim 23) of the Fn3 has been replaced. Spector teaches that the unfavorable electrostatic interactions of the residues in the loop region of

a protein destabilize a protein e.g., amino acids at positions 8, 9 and 36. Spector picked replacing residue at position 8. But suggests that other residues that unfavorably result in electrostatic interactions of residues at e.g., position 9 can be replaced. It would be within the ordinary skill in the art at the time the invention was made to choose other residues at e.g., position 7 as taught by Lipovsek. Spector suggests position 7 as the first position of the loop region. One would have a reasonable expectation of success in obtaining a stable FN3 as taught by Lipovsek since the unfavorable electrostatic interactions among the residues in the FN3 have been eliminated as taught by Spector. Spector suggests the general applicability of the technique to other compounds, as discussed above, not only to the test model protein derived from the dihydrolipoamide acetyltransferase component of the pyruvate dehydrogenase multienzyme complex from Bacillus stearothermophilus.

When a patent claims a structure already known in the prior art that is altered by the mere substitution of one element for another known in the field, the combination must do more than yield a predictable result. KSR v. Teleflex, 17 S. Ct. 1727, 82 USPQ 2d 1385 (2007). A patent for a combination which only unites old elements with no change in their respective functions

obviously withdraws what is already known into the field of its monopoly and diminishes the resources available to skillful men.

Appellant states that "obvious to try" is not the standard under 35 U.S.C. § 103. Specifically, trying each of numerous possible choices until one possibly arrived at a successful result, where the prior art gave either no indication of which parameters were critical or no direction as to which of many possible choices is likely to be successful, is an improper "obvious to try" standard. Applicant respectfully submits that the Examiner is improperly relying on an "obvious to try" standard by suggesting that the art worker could have tried each of numerous possible choices, i.e., the listing of amino acids, until the art worker possibly arrived at a successful result.

In reply, the positive teaching of Lipovsek as to the different amino acids that can be substituted in the Fn3 structure is not obvious to try. Rather, a modification that is obvious to do, given the positive residues e.g., positions 7, 9 and 23, encompassed in the range given by Lipovsek. The claims do not preclude any of the other amino acids taught by Lipovsek. In using the word “comprising”, appellant does not preclude the other amino acids in the range disclosed by Lipovsek, which includes the claimed positions. It has been long held that the use of the term "comprising' leaves a claim open for inclusion

of materials or steps other than those recited in the claims. Ex parte Davis, 80 USPQ 448. Furthermore, as held by the majority in Merck & Co. Inc. v. Biocraft Laboratories, Inc., 874 F.2d 804, 10 USPQ 2d 1843 (Fed. Cir. 1989), at 10 USPQ 2d 1846:

> That the '813 patent discloses a multitude of effective combinations does not render any particular formulation less obvious. This is especially true because the claimed composition is used for the identical purpose taught by the prior art. See In re Corkill, 771 F.2d 1496, 1500, 226 USPQ 1005, 1008 (Fed. Cir. 1985) (obviousness rejection of claims affirmed in light of prior art teaching that "hydrated zeolites will work" in detergent formulations, even though "the inventors selected the zeolites of the claims from among "thousands of compounds") (herein only in the binding region); In re Susi, 440 F.2d 442, 445, 169 USPQ 423, 425 (CCPA 1971) (obviousness rejection affirmed where the disclosure of the prior art was "huge, but it undeniably include[d] at least some of the compounds recited in appellants generic claims and it is of a class of chemicals to be used for the same purpose as appellant's additives").

Thus, the claimed stable Fn3 compound is obvious over the combined teachings of the prior art.

(11) Related Proceeding(s) Appendix

No decision rendered by a court or the Board is identified by the examiner in the Related Appeals and Interferences section of this examiner’s answer.

For the above reasons, it is believed that the rejections should be sustained.

Respectfully submitted,

/T. D. Wessendorf/

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Conferees:

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